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All-*Trans*-Retinoic Acid-Induced Myositis: A Description of Two Patients

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All-*trans*-retinoic acid (ATRA) induces complete clinical remissions in a high proportion of patients with acute promyelocytic leukemia and has become the standard induction therapy. Its use as a single agent results in short-lived remissions; thus, cytotoxic drugs are used for "consolidation" therapy. Side effects reported during treatment with ATRA include retinoic acid syndrome and Sweet's syndrome. Sweet's syndrome has been associated with acute myelogenous leukemia at presentation, but only two cases of Sweet's syndrome involving the musculoskeletal system in patients treated with ATRA have been described. We describe two additional patients with acute promyelocytic leukemia who had unexplained fever and myalgias (cutaneous lesions in one patient) during induction therapy with ATRA. Radiologic findings were similar to those in previously reported ATRA-associated Sweet's syndrome of the musculoskeletal system. The clinical course was characterized by a rapid resolution of the symptoms during treatment with dexamethasone. Recognition of the syndrome is important, especially considering the rapid resolution of symptoms after early institution of therapy with corticosteroids. Am. J. Hematol. 63:94–98, 2000. © 2000 Wiley-Liss, Inc.

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Acute promyelocytic leukemia (APL) (French-American-British [FAB] classification M-3) constitutes approximately 10% of acute myeloblastic leukemia in adults [1,2]. The morphologic findings in the classic hypergranular and microgranular variants are characteristic and allow easy recognition of the disease. The pathognomonic finding, however, is a balanced reciprocal translocation between the long arms of chromosome 17 and 15, t(15:17) [3]; rarely, variants such as t(11:17) are seen. The breakpoint on chromosome 17 disrupts a gene that encodes a nuclear receptor for retinoic acid (RAR-) [4]; its translocation to chromosome 15 results in fusion with a gene called PML, which may act as a transcription factor [5].

all-*trans*-retinoic acid (ATRA, tretinoin) has been reported to induce complete clinical remission in a high proportion of patients with APL [6–8]. However, because of short-lived remissions and rapid development of drug resistance [9], cytotoxic chemotherapy with anthracycline-based regimens is still used to improve long-term results. The initial biologic effects of ATRA are characterized by differentiation of the malignant cells into phenotypically mature myeloid cells [7,8].

A distinctive clinical syndrome characterized by fever, dyspnea, weight gain, pleural or pericardial effusions, and hypotension (retinoic acid syndrome, ATRA syndrome) has been reported in up to 25% of patients treated with ATRA [10]. Leukocytosis frequently precedes development of the ATRA syndrome, but the reaction may occur with a normal leukocyte count in up to a third of patients [10].

Sweet's syndrome (acute neutrophilic dermatosis) also has been reported in patients with acute myelogenous leukemia. In patients with APL, classic Sweet's syndrome has been reported to develop after treatment with ATRA [11–15]. Two patients recently have been de-

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TABLE I. Laboratory Values in Case 1*

	Normal value	Admission	Day 11	Day 17	Day 18	Day 27
Hemoglobin	12–15 g/dL	6.1	8.8	9.4	9.3	8.5
Leukocyte count	$(3.5–10.5) \times 10^9$/L	2.7×10^9/L	34.3×10^9/L	16.3×10^9/L	21.4×10^9/L	2.7×10^9/L
Platelets	$(150–450) \times 10^9$/L	9×10^9/L	19×10^9/L	14×10^9/L	18×10^9/L	92×10^9/L
INR	<1.2	1.32			1.25	
APTT	21–33 s	25			27	
Fibrinogen	175–350 mg/dL	203			314	
SFMC	Negative	Positive			Negative	
D-Dimer	<250	>500			>500	
Creatine kinase	38–176 U/L				135	
Creatine kinase-MB	<4.3 ng/mL				nd	

*APTT, activated partial thromboplastin time; nd, not done; SFMC, soluble fibrin monomer complex.

scribed with Sweet's syndrome involving the musculoskeletal system during treatment with ATRA [14].

We describe two additional patients in whom fever and myalgia developed after induction therapy with ATRA. One of these patients also had cutaneous abnormalities suggestive of Sweet's syndrome.

CASE REPORTS

Case 1

A 39-year-old white man presented with fatigue, dyspnea, fever, petechial rash, and pancytopenia. His laboratory data are shown in Table I. The patient had approximately 40% circulating myeloblasts. Bone marrow aspirate and biopsy confirmed a morphologic and cytogenetic diagnosis of APL (FAB M-3). There were approximately 80% promyelocytes and myeloblasts in a hypercellular marrow. Of 20 metaphases, 17 had the characteristic 15;17 translocation. Coagulation parameters improved with supportive care, including plasma, cryoprecipitate, intravenous unfractionated heparin, and platelet transfusions. Therapy with ATRA (45 mg/m^2 orally per day) was initiated.

The patient's leukocyte count increased to a maximum of 34.3×10^9 on day 11. He remained afebrile and was dismissed on day 17. On day 18, he was readmitted with a fever of 39°C, rigors, and mild dyspnea. His oxygen saturation was 98%, and the dyspnea resolved completely. He complained of exquisite pain on the right posterior tibialis muscle, which was warm and firm on palpation. Several 2-mm erythematous papular and pustular lesions were noted on his extremities and trunk. A deep vein thrombosis was ruled out with ultrasonography. Antibiotic therapy was started with a third-generation cephalosporin. In the following days, localized, very painful, and bilateral nodular lesions developed in his quadriceps femori, posterior tibial muscles, and right biceps. The patient remained febrile (38–39°C), and no source of infection could be established. Blood and urine cultures remained negative. The creatine kinase value was within normal limits. On day 23, magnetic resonance imaging of both lower extremities showed focal areas of increased T2 signal within the quadriceps muscles bilaterally, within most of the left sartorius and soleus muscles, and in all compartments of the right lower leg. In addition, there was thickening of the adjacent fascia with associated subcutaneous edema (Fig. 1). A working diagnosis of ATRA-induced musculocutaneous Sweet's syndrome was made.

Treatment with ATRA was discontinued, and dexamethasone therapy (8 mg/12 hr) was started on day 23. There was prompt resolution of the pain and fever. The cutaneous lesions improved dramatically. On day 25, therapy with ATRA (45 mg/m^2 orally per day) was restarted, and the patient was dismissed from the hospital on day 27. Use of dexamethasone was discontinued on day 36. The patient's symptoms did not recur. A bone marrow aspirate and biopsy obtained on day 38 confirmed a morphologic and cytogenetic complete remission. Use of ATRA was discontinued on day 39.

Case 2

A 35-year-old white woman presented with diarrhea, palpitations, epistaxis, and bruising of 1 week's duration. Her laboratory data are shown in Table II.

There were approximately 70% leukemic blasts in the peripheral blood. A morphologic and cytogenetic diagnosis of APL was confirmed on a bone marrow aspirate and biopsy. There were approximately 90% myeloblasts and abnormal promyelocytes on the bone marrow aspirate. Cytogenetic studies confirmed the presence of the characteristic 15;17 translocation in 9 of 10 metaphases, and 82% of 200 interphase nuclei had the characteristic fusion PML and RARA signals on fluorescent in situ hybridization studies.

Therapy with ATRA (45 mg/m^2 orally per day) was started. The ongoing coagulopathy was treated with appropriate plasma-derived products, and intravenous unfractionated heparin was administered through day 6 of ATRA therapy and discontinued after resolution of the coagulation abnormalities.

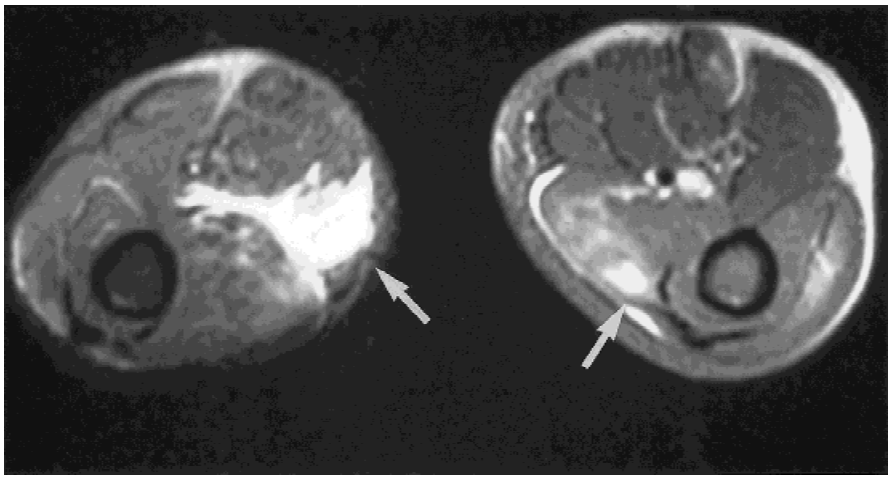

Fig. 1. Case 1. Magnetic resonance imaging scan of lower extremities (thighs), demonstrating focal areas of T2 signal within the quadriceps bilaterally (arrows), within most of the left sartorius and soleus muscles, and in all compartments of the right lower leg (not shown). There is thickening of adjacent fascia with associated subcutaneous edema. Findings are consistent with edema or inflammation.

TABLE II. Laboratory Values in Case 2*

	Normal value	Admission	Day 5	Day 9	Day 14	Day 17	Day 20	Day 21	Day 24
Hemoglobin	12–15 g/dL	6.9	10	9.3	11.3	8	9.1		
Leukocyte count	$(3.5–10.5) \times 10^9$/L	8.0×10^9/L	43.3×10^9/L	30.8×10^9/L	2.6×10^9/L	1.6×10^9/L	2.5×10^9/L		
Platelets	$(150–450) \times 10^9$/L	6.0×10^9/L	11.0×10^9/L	23.0×10^9/L	17×10^9/L	33×10^9/L	19×10^9/L		
INR	<1.2	1.21			1.05		1.25		
APTT	21–33 s	21			25		28		
Fibrinogen	175–350 mg/dL	77	226	290	427		526		
SFMC	Negative	Positive					Positive		
D-Dimer	<250	>500	250–500						
Creatine kinase	38–176 U/L						348	355	69
Creatine kinase-MB	<4.3 ng/ML						1		

*APTT, activated partial thromboplastin time; SFMC, soluble fibrin monomer complex.

Because of a progressive increase in the patient's leukocyte count, idarubicin (12 mg/m^2) was administered intravenously on days 5, 7, 9, and 11. On day 9 of ATRA therapy, the patient became febrile, with temperatures of up to 39.5°C, and complained of a sore throat. Aside from pharyngeal erythema and tender cervical lymphadenopathy, her physical examination was unrevealing. Despite a significant increase in temperature, the patient did not appear clinically septic. No pathogenic organisms were isolated on repeated blood and urine cultures. Antibiotic treatment with third-generation cephalosporins and vancomycin was started, and the patient became afebrile on day 14 (day 6 of antibiotics). On day 17, the fever recurred (39°C) and persisted despite additional antibiotics for anaerobic coverage.

On day 20, the patient complained of severe bilateral anterior leg pain. She denied similar pains in other muscles. On examination, both tibialis anterior muscles were firm and tender. Detailed examination revealed no other cutaneous lesions. Creatine kinase levels were increased (Table II). A working diagnosis of ATRA-related myositis was made, and daily treatment with intravenous dexamethasone (10 mg/day) was started. ATRA was withheld for 1 day. On day 21, the patient's fever resolved, and in the ensuing days her pain decreased and the muscles on the anterolateral compartments of her legs felt softer and less tender. The creatine kinase value was 69 U/L on day 24. On day 24, magnetic resonance imaging of her legs showed abnormal T2 signal and enhancement of the tibialis anterior muscles bilaterally with associated enlargement of these muscles and central areas of non-enhancement consistent with necrosis. Some edema in the subcutaneous fat was noted (Fig. 2). On day 24, use of dexamethasone was discontinued. The same day, she experienced similar recurrent pain in her legs. Examination once again showed focal firmness and tenderness, predominantly in the anterolateral compartments of her legs as well as in the gastrocnemius muscles and Achilles tendon. Use of ATRA was again discontinued (on day 24, and not restarted), and therapy with oral dexamethasone (10 mg every 12 hr) was started. Once again, this resulted in a marked improvement in the patient's symptoms and resolution of the firmness and muscle tenderness.

The patient was dismissed from the hospital, and the dexamethasone was continued on a tapering schedule over 1 week. On day 30, bone marrow studies confirmed a complete morphologic and cytogenetic remission. Magnetic resonance imaging of both lower legs on day 47 showed evidence of resolution in the amount of signal

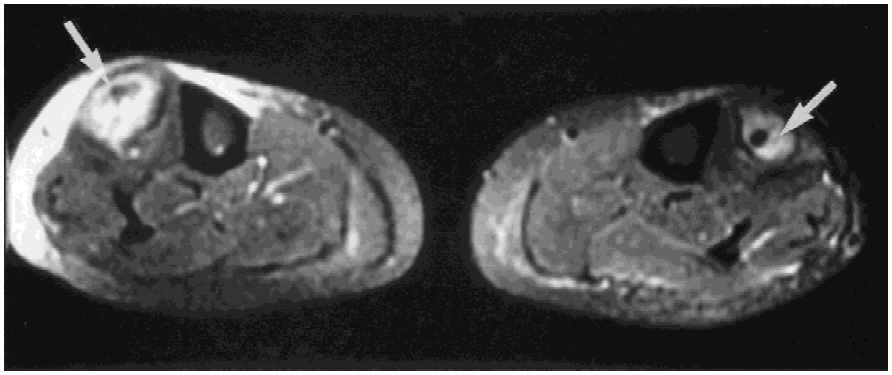

Fig. 2. Case 2. Magnetic resonance imaging scan of lower extremities (legs), showing abnormal T2 signal and enhancement in tibialis anterior muscles bilaterally (arrows). There is enlargement of these muscles and central area of non-enhancement consistent with necrosis.

abnormality, the signal abnormalities being primarily limited to the central portion of the muscle belly, containing some increased T1 and T2 signal.

DISCUSSION

ATRA has become standard induction therapy for APL. Although ATRA initially was considered benign, the number of reports of toxicities associated with this therapy is increasing. Reported complications of ATRA in APL include headaches, intracranial hypertension, hepatic toxicity, thrombosis, congestive heart failure, pleural and pericardial effusions [16], the retinoic acid syndrome [10], and Sweet's syndrome [11–14].

Sweet's syndrome, or acute febrile neutrophilic dermatosis, was first described by Dr. R. D. Sweet in 1964 [17]. It is characterized by painful erythematous papules, pustules, plaques, and nodules, usually in association with fever, arthralgias, and neutrophilic dermatosis [17,18]. The cause of the syndrome is as yet unknown [19,20], but approximately 25% of cases have parainflammatory and paraneoplastic findings [20]. The syndrome has been reported to respond rapidly to systemic therapy with corticosteroids, but it recurs in 25% of cases [20]. Sweet's syndrome as a complication of the treatment of APL with ATRA [11–14] is rare. To our knowledge, there has been only one report, including two patients, of Sweet's syndrome involving the musculoskeletal system during treatment with ATRA [14]. The patients had been treated with ATRA for 9 and 17 days before the development of symptoms and cutaneous lesions.

In general, patients with leukemia are severely neutropenic at presentation, and after myelosuppressive therapy they are at high risk for infectious complications. Corticosteroids are the mainstay of therapy for complications related to ATRA, but they will suppress fevers that occur in response to infections. Thus, although adequate antibiotic coverage for potential pathogenic organisms is typically provided for neutropenic fevers, the duration of corticosteroid therapy should be minimized.

In patients with ATRA-induced Sweet's syndrome, therapy with corticosteroids results in prompt resolution of systemic symptoms and cutaneous lesions. Because of the rarity of the syndrome, information is lacking on the role of discontinuing ATRA therapy and the duration of corticosteroid therapy in patients with ATRA-induced Sweet's syndrome. In the first patient described by Christ et al. [14], ATRA therapy was discontinued; in the second patient, ATRA therapy was continued after the addition of prednisolone, with no adverse outcome.

One of our patients (case 1) presented on day 18 with unexplained fever, muscle pain, and cutaneous abnormalities suggestive of Sweet's syndrome. Although no biopsy was performed, the magnetic resonance imaging findings were similar to those described by Christ et al. [14]. Treatment with ATRA was withheld for 2 days, but therapy with dexamethasone (8 mg/12 hr) was started, and there was rapid improvement of his symptoms. The dexamethasone therapy was continued for 36 days, and there were no adverse outcomes despite continuing the ATRA therapy for an additional 21 days.

In our other patient (case 2), unexplained fever and muscular pain developed on day 20. No evidence of cutaneous involvement was found. However, her serum creatine kinase value was increased, and because her presentation was similar to that of the other patient, we elected to start dexamethasone therapy (10 mg/day). She also improved rapidly. The ATRA therapy was withheld for 1 day, and use of corticosteroids was discontinued after 3 days. On the fourth day, recurrent symptoms developed, and they promptly resolved with resumption of the corticosteroid therapy. The use of ATRA was not resumed. She experienced no recurrent symptoms on tapering of the corticosteroids over 1 week.

It remains unclear why the muscles of the lower limbs were preferentially involved in both of our patients.

The mechanism of retinoic acid syndrome and, more specifically, Sweet's syndrome remains speculative, but it is likely multifactorial, with environmental factors and abnormalities in leukocytes, surface integrins and their receptors, and cytokines playing a role.

Sweet's syndrome has been reported to occur in sun-exposed areas and venipuncture sites [21]. This was not

the case in one of our patients (case 1), in whom the lesions occurred in unexposed areas.

ATRA induces terminal differentiation of leukemic cells [22], which may infiltrate various organs [23] and set up an inflammatory reaction.

In addition, granulocyte colony-stimulating factor (G-CSF) levels increased in a patient before development of Sweet's syndrome [24], and Sweet's syndrome developed in a patient receiving chemotherapy after three doses of G-CSF [25]. Inappropriate cytokine secretion [26] likely plays a major role in this syndrome given the systemic manifestations, including fevers, but this remains to be further defined.

In addition, the role of adhesion receptors has recently been explored. Aggregation of APL cells, exposed to ATRA in vitro, increases in a dose- and time-dependent fashion and is dependent on integrity of ligands such as lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecules (ICAM-2) and their receptors. Addition of corticosteroids inhibits this aggregation, which is consistent with the clinical response in vivo [27].

Further study into the exact pathogenesis is needed to define factors that predict the development of retinoic acid syndrome, which may eventually lead to prophylactic and therapeutic alternatives.

Recognition of the side effects and complications of treatment of APL with ATRA is of practical importance. Unexplained fever, myalgias, and, in one of our cases, cutaneous symptoms alerted us to the possibility of ATRA-induced side effects. If myalgias develop during treatment with ATRA, awareness of its possible side effects is important, especially considering the impressive resolution of symptoms after therapy with corticosteroids, thus permitting continuation of the use of ATRA for treatment of the leukemia.

REFERENCES

1. Stone RM, Mayer RJ. The unique aspects of acute promyelocytic leukemia. J Clin Oncol 1990;8:1913.
2. Mayer RJ, Schiffer CA, Peterson BA, Budman DR, Silver RT, Rai KR, Cornwell GG, Ellison RR, Maguire M, Berg DT, Davis RB, McIntyre OR, Frei E III. Intensive postremission therapy in adults with acute nonlymphocytic leukemia using various dose schedules of ara-C: A progress report from the CALGB. Cancer and Leukemia Group B. Semin Oncol 1987;14(Suppl 1):25.
3. Larson RA, Kondo K, Vardiman JW, Butler AE, Golomb HM, Rowley JD. Evidence for a 15;17 translocation in every patient with acute promyelocytic leukemia. Am J Med 1984;76:827.
4. Chomienne C, Ballerini P, Balitrand N, Huang ME, Krawice I, Castaigne S, Fenaux P, Tiollais P, Dejean A, Degos L, de The H. The retinoic acid receptor α gene is rearranged in retinoic acid-sensitive promyelocytic leukemias. Leukemia 1990;4:802.
5. Kakizuka A, Miller WH Jr, Umesono K, Warrell RP Jr, Frankel SR, Murty VV, Dmitrovsky E, Evans RM. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR α with a novel putative transcription factor, PML. Cell 1991;66:663.
6. Huang ME, Ye YC, Chen SR, Chai JR, Lu JX, Zhoa L, Gu LJ, Wang ZY. Use of all-*trans*-retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988;72:567.
7. Castaigne S, Chomienne C, Daniel MT, Ballerini P, Berger R, Fenaux P, Degos L. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood 1990;76:1704.
8. Warrell RP Jr, Frankel SR, Miller WH Jr, Scheinberg DA, Itri LM, Hittelman WN, Vyas R, Andreeff M, Tafuri A, Jakubowski A, Gabrilove J, Gordon MS, Dmitrovsky E. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-*trans*-retinoic acid). N Engl J Med 1991;324:1385.
9. Frankel SR, Eardley A, Heller G, Berman E, Miller WH Jr, Dmitrovsky E, Warrell RP Jr. All-*trans*-retinoic acid for acute promyelocytic leukemia. Results of the New York Study. Ann Intern Med 1994;120:278.
10. Frankel S, Weiss M, Warrell RP Jr. A "retinoic acid syndrome" in acute promyelocytic leukemia: Reversal by corticosteroids. Blood 1991;78(Suppl):380a.
11. Tomas JF, Escudero A, Fernandez-Ranada JM. All-trans retinoic acid treatment and Sweet syndrome (letter). Leukemia 1994;8:1596.
12. Piette WW, Trapp JF, O'Donnell MJ, Argenyi Z, Talbot EA, Burns CP. Acute neutrophilic dermatosis with myeloblastic infiltrate in a leukemia patient receiving all-*trans*-retinoic acid therapy. J Am Acad Dermatol 1994;30:293.
13. Cox NH, O'Brien HA. Sweet's syndrome associated with trans retinoic acid treatment in acute promyelocytic leukaemia. Clin Exp Dermatol 1994;19:51.
14. Christ E, Linka A, Jacky E, Speich R, Marincek B, Schaffner A. Sweet's syndrome involving the musculoskeletal system during treatment of promyelocytic leukemia with all-*trans*-retinoic acid. Leukemia 1996;10:731.
15. Arun B, Berberian B, Azumi N, Frankel SR, Luksenburg H, Freter C. Sweet's syndrome during treatment with all-trans retinoic acid in a patient with acute promyelocytic leukemia. Leuk Lymphoma 1998;31:613.
16. Warrell RP Jr, de The H, Wang ZY, Degos L. Acute promyelocytic leukemia. N Engl J Med 1993;329:177.
17. Sweet RD. An acute febrile neutrophilic dermatosis. Br J Dermatol 1964;76:349.
18. Sweet RD. Acute febrile neutrophilic dermatosis—1978. Br J Dermatol 1979;100:93.
19. Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: Review of the world literature. J Clin Oncol 1988;6:1887.
20. von den Driesch P. Sweet's syndrome. J Am Acad Dermatol 1994;31:535.
21. Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: Review of the world literature. J Clin Oncol 1988;6:1887.
22. Castaigne S, Chomienne C, Daniel MT, Ballerini P, Berger R, Fenaux P, Degos L. all-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood 1990;76:1704.
23. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med 1992;117:292.
24. Reuss-Borst MA, Muller CA, Waller HD. The possible role of G-CSF in the pathogenesis of Sweet's syndrome. Leuk Lymphoma 1994;15:261.
25. Park JW, Mehrotra B, Barnett BO, Baron AD, Venook AP. The Sweet syndrome during therapy with granulocyte colony-stimulating factor. Ann Intern Med 1992;116:996.
26. Eghrari-Sabet JS, Hartley AH. Sweet's syndrome: An immunologically mediated skin disease? Ann Allergy 1994;72:125.
27. Larson RS, Brown DC, Sklar LA. Retinoic acid induces aggregation of the acute promyelocytic leukemia cell line NB-4 by utilization of LFA-1 and ICAM-2. Blood 1997;90:2747.